REMARKS

This responds to the Office Action mailed on April 29, 2005, and the documents cited therewith.

No claims were amended or added; claims 1-5, 15-18, and 27-43 were canceled previously; and claims 19-26 stand withdrawn under 37 C.F.R. § 1.142(b); as a result, claims 6-14, 19-26, and 44-58 are now pending in this application.

Restriction Requirement

Applicants respectfully request reconsideration and withdrawal of the finality of the restriction requirement. The Examiner has referred to the Office Action dated August 31, 2004 for his reasons as to why Applicants' traversal was not persuasive. However, the August 31, 2004 Office Action is the restriction requirement itself. Applicants reiterate that both claim groups created by the Examiner are classified identically in Class 514, subclass 563, and that a search of one group will necessarily locate the art relevant to the other group. Therefore, the Examiner's statement in the restriction requirement that the groups "have a separate status in the art as shown by their different and separate subject matter" is a conclusory statement that does not address Applicants' reasons for traversal. Restriction requirement at page 2.

By using the same arguments as in the restriction requirement to respond to Applicants' traversal, the Examiner has not addressed the specific points regarding serious search burden raised in Applicants' traversal. Without establishing serious search burden, restriction is improper. MPEP § 803. Accordingly, Applicants' submit that the finality of the restriction requirement is improper and premature, and respectfully request withdrawal of the finality.

Provisional Obviousness-type Double Patenting Rejection

Claims 6-14 and 44-58 were provisionally rejected over claims 10-12 of copending Application No. 10/903,500 under the judicially created doctrine of obviousness-type double patenting.

Applicants request that the Examiner hold this rejection in abeyance in this application until there is an indication of allowable subject matter.

Rejection Under 35 U.S.C. § 112, First Paragraph – Scope of Enablement

Claims 6-14 and 44-58 were rejected under 35 U.S.C. § 112, first paragraph because the specification, while being enabling for a method of protecting breast tissue against damage from radiation therapy, comprising administering to a mammalian subject afflicted with breast cancer a composition comprising glutamine, a carbohydrate (sucrose), and a sugar alcohol (sorbitol), does not reasonably provide enablement for protecting non-mucosal tissue against damage from radiation therapy wherein the subject is afflicted with other types of cancer or the glutamine is combined with other carbohydrates to increase the absorption of glutamine or prevents increased breast density and edema. This rejection is respectfully traversed.

Applicants note initially that the Examiner has employed the infamous *Biotech Squeeze*, which long ago has been held improper by the USPTO: the Examiner on one hand considers Applicants' specification non-enabled for the full scope of the claims under § 112 first paragraph because of the alleged unpredictability in "the art to which the present invention relates," and on the other hand finds the cited documents sufficiently enabling for him to conclude that "one skilled in the are [sic – art] would have assumed the instant oral glutamine of the two cited references would protect ... non-mucosal tissues" and to reject some of the same claims (including claim 6, which recites *inter alia* administering a composition comprising an effective amount of glutamine to a mammalian subject afflicted with cancer) for obviousness under § 103. Office Action at pages 5 and 8.

The two cited documents disclose more than breast cancer. Klimberg et al. refers to rat sarcoma at page 422 and to bone marrow transplant patients and solid tumor patients at page 423. Skubitz et al. refers to patients with various cancers (Kaposi's sarcoma, osteosarcoma, soft tissue sarcoma, squamous cell carcinoma of the head and neck) at page 225. Therefore, if the cited documents are sufficiently enabling to one skilled in the art to reject the claims for obviousness, then Applicants' specification would also enable those claims without undue experimentation.

Applicants respectfully submit that the Examiner cannot have it both ways. The solution to the *Biotech Squeeze* frequently enunciated publicly by USPTO representatives is that the Examiner must choose to make or maintain one or the other rejection, but not both an art rejection and an enablement rejection of the same claims.

When rejecting a claim under the enablement requirement of section 112, the Examiner bears the "initial burden of setting forth a reasonable explanation as to why [he/she] believes that the scope of protection provided by [the] claim is not adequately enabled by the description of the invention provided in the specification." *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The Examiner bears the burden of providing evidence or technical reasoning to substantiate his doubts that the specification is not enabling with respect to the scope of a claim sought to be patented. *Ibid. See also* MPEP § 2164.04. Without evidence or technical reasoning to doubt the truth of the statements made in the application, the application must be considered enabling. *Ibid.* In addition, an enablement rejection should be stated with a full development of the reasons rather than by a mere conclusion coupled with some stereotyped expression. MPEP § 706.03.

The Examiner touched briefly on some of the *Wands* factors at pages 4 to 6 of the Office Action. However, the *Wands* analysis is flawed because the Examiner's conclusions appear mainly to be doubts unsubstantiated by evidence or technical reasoning, and appear to be mere conclusions coupled with stereotyped expression, specifically proscribed by MPEP § 706.03. Thus, for example, at page 5 the Examiner stated, "[i]t is clear the art to which the present invention relates is highly unpredictable and unreliable with respect to conclusions drawn from laboratory data extrapolated to clinical efficacy." It is clear that this is an unsubstantiated and conclusory statement that contradicts the Examiner's own statements made in the obviousness rejection that the routineer would have assumed oral glutamine would protect non-mucosal tissues. The Examiner is reminded that without evidence or technical reasoning to doubt the truth of the statements made in the application, the application must be considered enabling.

The Examiner also stated "[t]here are no examples showing the instant composition will, in fact, prevent increased breast density or prevent edema." Office Action at page 5. The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. MPEP § 2164.02 (citing *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). One skilled in the art would know that edema (swelling from excessive accumulation of serous fluid in tissue) may be induced by radiation therapy and that radiation-induced edema of the breast manifests as increased breast density. See R. Krishnamurthy et al., *Radiographics* **1999**,

19: S53-S62, copy attached. Therefore, one would expect protection against radiation-induced edema and increased breast density from a composition that protects non-mucosal tissue against damage from radiation therapy. There is no need to exemplify a method which presumes knowledge of the art and which would not require undue experimentation to practice by virtue of that knowledge.

The Examiner stated further that "[t]he working examples are limited to the administration [of] a composition comprising glutamine with sucrose and a sugar alcohol (sorbitol)(Example 1) to non-mucosal tissue (breast tissue) against damage from radiation therapy wherein the subject is afflicted with breast cancer only (Example 4)." *Ibid.* Applicants need not describe and exemplify all actual embodiments. MPEP § 2164.02. Applicants submit that their specification provides ample guidance for the routineer to make and use the full scope of their claimed invention without undue experimentation. Example 1 provides sufficient guidance for the routineer to make compositions containing other carbohydrates and sugar alcohols. Example 2 is a method for determining cellular uptake and the permeability-enhancing effect of a sucrose-containing vehicle, which method would be similarly useful for vehicles containing other carbohydrates. In *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988), the court ruled that since one embodiment and the method to determine dose response was set forth in the specification, the specification was enabling. This fact pattern is entirely analogous to Applicants' disclosure of Example 1 and a method for determining cellular uptake and the permeability-enhancing effect of a sucrose-containing vehicle.

Furthermore, as the documents cited by the Examiner in the obviousness rejection under § 103 show, glutamine supplementation has been used to treat a variety of cancers, including breast cancer. Therefore, one would expect the present method of protecting non-mucosal tissue against damage from radiation therapy, which comprises administering a therapeutically effective amount of glutamine to a mammalian subject afflicted with cancer and treated with radiation therapy, to be useful against a variety of cancers as well. The Examiner's statement that a considerable quantity of experimentation would be necessary to practice the full scope of Applicants' invention is simply inconsistent with the knowledge in the art.

Finally, the Examiner has not established why a mere recitation of the nature of the invention and the high skill level of those in the art contribute to a determination of undue

experimentation. Furthermore, the Examiner has not addressed the state of the art; he addressed only the alleged unpredictability of the art. Certainly a proper analysis of the state of the art would have to include the very documents cited by the Examiner in the § 103 rejection, and as noted above, these documents would have pointed away from the need for undue experimentation to enable Applicants' invention.

Withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. § 103

Claims 6, 8, 9, 12-14, 44-47, and 54-58 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Klimberg et al. or Skubitz et al. The Examiner stated that "[b]oth references, individually, teach the administration of an oral glutamine supplement or composition will protect the host or mammal's gut from injury caused by radiation or chemotherapy," and "one skilled in the are [sic –art] would have assumed the instant oral glutamine of the two cited references would protect the non-mucosal tissues of the applicants since the [sic] most animals or mammals or subjects who received radiation therapy have nauseated stomachs and the administration of oral glutamine decrease [sic] the severity of the radiation or chemotherapy induced nausea in the absence of evidence to the contrary." Office Action at page 8 (emphasis added). This rejection is respectfully traversed.

First, Skubitz et al. discloses (p. 227) that oral glutamine supplementation decreases the severity of stomatitis and esophagitis induced by chemotherapy. Protection of the gut from radiation is disclosed in the abstract only as a possibility. Second, the basis of the rejection is unclear. The Examiner appears to be saying that reduction of nausea in cancer patients receiving radiation therapy for cancer of non-mucosal tissue would render obvious protection of the non-mucosal tissue against damage from radiation therapy. Clarification of this rejection is requested.

Nausea, if it even arises at all after radiation therapy of non-mucosal tissue, is a side effect, and reduction of nausea is not equivalent to protection of the non-mucosal tissue itself from the radiation. Moreover, nausea after radiation therapy of non-mucosal tissue is rare; nausea is an occasional side effect observed especially after radiation delivered to the abdominal area. See the enclosed website articles from breastcancer.org (see point 4 under Myths about

Radiation Therapy) and cancerconsultants.com (see Nausea/vomiting at page 6). Accordingly, it is a conclusory overstatement to say most animals or mammals or subjects who received radiation therapy have nauseated stomachs. Therefore, the rejection appears based on an erroneous assumption by the Examiner.

Furthermore, the Federal Circuit has held that core factual findings in patentability determinations must be supported by concrete evidence in the record in support of these findings. Reliance by the Examiner on what "one skilled in the art would have assumed" is not concrete evidence. *In re Zurko*, 258 F.3d 1379, 59 USPQ2d 1693 (Fed. Cir. 2001); *In re Lee*, 277 F.3d 1338, 61 USPQ2d 1430 (Fed. Cir 2002); *In re Beasley*, 117 Fed. Appx. 739, 2004 WL 2793170 (Fed. Cir.). Accordingly, the rejection is improper. Withdrawal of this rejection is respectfully requested.

CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' attorney at (612) 373-6903 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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